RESPONSE

I. Status of the Claims

Claims 1, 4, 5, 8 and 21 have been amended. Claim 3 has been cancelled without prejudice or disclaimer. Claims 1, 2, 4-6, 8 and 21 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

II. Support for the Amended Claims

Claim 1 has been amended to further clarify the claim, and to recite specifically 100 bases. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in Claim 1 as originally filed and at page 11, line 22 of the specification as filed.

Claims 4, 5, 8 and 21 have been amended to reflect the cancellation, without prejudice or disclaimer, of claim 3. Amended claims 4, 5, 8 and 21 are supported by the specification as originally filed, with particular support being found at least in original claims 4, 5, 8 and 21 respectively.

As amended claims 1, 4, 5, 8 and 21 are fully supported by the specification and claims as originally filed, do not constitute new matter and place the case in better condition for allowance or appeal. Entry therefore is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. §§ 102

Claims 1, 3-6 and 21 stand rejected under 35 U.S.C. § 102(a)as being anticipated by EST accession no. AI399758 which is alleged to contain 64 contiguous bases of SEQ ID NOS: 1 and 3. Applicants respectfully submit that as the best art is properly cited against a claim, this EST should have been cited in a previous action. It also appears that the Action is trying to cite the entire NCI-CGAP database as possibly containing molecules that might hybridize to the sequences of the present invention. It is Applicants belief that such a rejection, based not on evidence but on

possibilities and supposition, is not proper under 35 U.S.C. § 102. However, while Applicants in no way agree with this rejection, as Applicants have amended Claim 1 and cancelled Claim 3 without prejudice or disclaimer, this rejection has been rendered moot.

IV. Rejection of Claims Under 35 U.S.C. §§ 101/112

Claims 1-6, 8 and 21 stand rejected under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The Action questions Applicants assertion of utility based on homology to proteins of known function, citing articles by Bowie *et al* (Science 1990 Mar; 247:1306-1310), Rudinger (Peptide Hormones 1976; June; pages 1-7), Everett *et al* (Nat Genetics 1997; 17:411-22), Scott *et al* (Nat Genetics 1999 Apr; 21:440-443) and Bork (Genome Research *10*:398-400, 2000). Applicants note that several of the cited articles are quite old, and thus one must question whether, for example, articles published 27 years ago or even 13 years ago correctly represents the current state of the art in 2003.

Typical of the articles the action cites is Bork (Genome Research *10*:398-400, 2000), which is cited as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action on page 6, line 14-15, directs attention to page 400, on which it notes that classical predication methods have an error rate of 82%.

Applicants note that it is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1, on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Applicants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on

page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement.

The PTO has repeatedly attempted to deny the utility of nucleic acid sequences based on a small number of spurious publications that call into doubt the usefulness of bioinformatic predictions, of which these two articles are merely the latest examples. However, without going into the merits (or lack thereof) of all of the cited articles, Applicants point out that the lack of 100% unanimous agreement on the usefulness of bioinformatic prediction programs is **completely irrelevant** to the question of whether the claimed nucleic acid sequence has a substantial and specific utility. Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Applicants submit that the overwhelming majority of those of skill in the relevant art would **believe** bioinformatic prediction to be a powerful and useful tool, as evidenced by hundreds if not thousands of journal articles, and would thus **believe** that Applicants sequence is a serine protease. As this is the standard for meeting the utility requirement of 35 U.S.C. § 101, Applicants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

The Final Action disagrees with Applicants' logical assertion, based on the evidence, that the sequences of the present invention encodes a novel human protein containing leucine-rich repeat (LRR) domains and is involved in signal transduction. In previous responses, Applicants have provided several pieces of evidence that those of skill in the art would find Applicants' assertion credible. The Final Action disregarded Applicants position regarding Fong and states that "From a functional perspective, the folding structural similarity is much more reliable than overall sequence homology"(page 7, lines 10-12). Applicants presently include additional evidence, as **Exhibit C**, that the sequences of the present invention share 100 percent homology over an extended region with the sequences present in the leading scientific repository for biological sequence data (GENBANK), and has been annotated by third party scientists *wholly unaffiliated with Applicants* when faced with the same information, would and did identify the sequences of the present invention as a human protein containing LRR domains. This evidence demonstrates that the sequences of the present invention are 100% homologous to those of Homo sapiens, leucine-rich repeat-containing 2 (LRRC2: GenBank nucleotide accession no. BC029118 and protein accession no. Q9BYS8, the details of which are provided as **Exhibit D**)

located on human chromosome 3. While applicants do not necessarily agree with the Examiner's arguments, none the less as this homology is 100%, these proteins would be expected to share 'folding structural similarity', which the action identifies as more reliable predictor of shared function.

Thus those of skill in the art agree with Applicants' assertion and would, therefore, clearly find Applicants' assertion credible. Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Final Action appears to be arguing that Applicants have not disclosed a physiological role for said protein. Applicants assert the polypeptide is a novel human leucine rich repeat protein and in Section 2 of the specification disclose that such proteins play important roles in, *inter alia*, signal transduction. It is Applicants' position that patentable utility is distinct from, and does not require a knowledge of, physiological function. In fact, historically patentable utility has not required a knowledge of how the invention functions does not require It is also Applicants' position that unless Applicant is claiming a physiological function, evidence of a physiological function is not required to demonstrate patentable utility. In fact, structural claims such as those of the present application are sufficiently supported by structural disclosure as defined by 35 U.S.C. § 101 and related case law. Furthermore, the Action also seems to be implying that because Applicants' sequence is novel, it lacks utility. Applicants are unaware of any patent law, patent rule, or ruling from the Supreme Court or the Court of Appeals for the Federal Circuit that supports this position. Applicants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility.

The Action also discounts Applicants' assertion regarding the use of the presently claimed polynucleotides on DNA chips, based on the position that such a use would allegedly be generic.

Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Additionally, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications, further discounting the Examiner's position that such uses are "generic". Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer,

HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the utility the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences (see evidence below). In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated

empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit E**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 8 exons spread non-contiguously along a region of human chromosome 3, at approximately 3p21. which are contained within clone AC104304.2. Thus clearly one would not simply be able to identify the 8 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were. It should also be noted that the gene encoding LRRC2 maps to the same location on the human genome, further supporting the relationship between the sequences of the present invention and LRRC2.

Additionally, the real world utility of the present invention is demonstrated by results obtained when a knockout mouse was made in which the mouse gene encoding the ortholog of the sequences of the present invention (human LRRC2) was disrupted by homologous recombination. These knockout mice were subject to a medical work-up using an integrated suite of medical diagnostic procedures designed to assess the function of the major organ systems in a mammalian subject.

Disruption of the mouse gene of the present invention and thus elimination of the protein it encodes, resulted in a notable decrease in the startle response of the homozygous (-/-) deficient mice. This clearly provides evidence that the nucleic acid and protein of the present invention have a biological function, which when removed results in a notable deficiency. This further supports Applicants assertion that the molecules of the present invention as well as agonists or antagonists directed at them can be used to diagnose and treat physiological disorders.

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different

standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in previous Applicant responses, the presently claimed invention has been shown to have a substantial, specific, credible and well-established utility and that the rejection of pending claims 1,2, 4-6, 8 and 21 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

V Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-6, 8 and 21 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse. Applicants submit that as the claims have been shown to have a specific, substantial, credible and well established utility, as detailed in the section above, Applicants respectfully request that the rejection of pending claims 1,2, 4-6, 8 and 21 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Li have any questions or comments, or

believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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